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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,492	02/12/2001	Jianlin Gong	20363-004 (DFCI-4)	7050

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,492	NICOLETTE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32, 36-39, 42, 46-49, 52-55, 84, 89, and 90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,36-39,42,46-49,52-55,84,89 and 90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12/15/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment, Declaration, and Remarks filed 5/14/04 have been entered. Claims 35 and 45 have been canceled. Claims 32, 36, 42, 46, 52-54, 84, and 89 have been amended. Claims 32, 36-39, 42, 46-49, 52-55, 84, 89, and 90 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 5/14/04 response would be addressed to the extent that they apply to current rejection.

Change of Inventorship

In view of the papers filed 5/14/04, the inventorship in this nonprovisional application has been changed by the deletion of Charles A. Nicolette and Bruce L. Roberts.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Specification

Applicants indicated they filed replacement formal drawings for figures 1-13. However, it is noted that the document is missing from the 5/14/04 submission. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32, 36-39, 42, 46-49, 52-55, 84, 89, and 90 stand and newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record and following.

Concerning the efficacy of treating cancer in humans with the claimed cell population, Applicants argue that the specification as filed discloses that the claimed immune effector cells induced cytolysis of several types of human cancer cells. Applicants further assert that the Examiner has mischaracterized the post-filing Parkhurst publication, because the hybrids of Krause and Kikuchi publications cited by Parkhurst cannot be compared to the hybrid cells of the present invention, and because Krause et al use gamma-irradiated primary tumor cells for fusion, and the fusion efficacy of the Kikuchi reference is lower than the efficacy of the present invention.

The arguments are fully considered but they are not persuasive because as taught by *Krause* (J Immunol 2002;25:421-8) and *Kikuchi et al* (Cancer Immunol Immunother 2001;50:337-44), the *ex vivo* experimental data do not correlate well with the *in vivo* cancer killing effect. For example, *Kruse et al* teach the fusion cell product lyses tumor cells in a mixed lymphocyte tumor cell culture, but once delivered to a subject, the clinical efficacy is insufficient. Concerning the types of hybrid cells disclosed

by *Krause* and *Kikuchi et al*, they are encompassed by the instant claims because the claims do not place any limitation on the efficacy or means of fusion, and the claims do not exclude using gamma-irradiated tumor cells as fusion partner. It is noted that irradiating tumor cells are a common practice in the art for safety concerns.

The amended claims are directed to a substantially pure *cytotoxic* population of antigen-specific immune effector cells comprising CD4+ T cells. However, the specification fails to teach that the CD4+ T cells are cytotoxic. Applicants used the publication of *Parkhurst et al* as evidence for the presence of CD4+ cells, however, *Parkhurst et al* teach that the CD4 population is helper cells (Th), they do not teach that the CD4+ T cells are cytotoxic. Although the specification teaches that anti-CD4 treatment would reduce or deplete the tumor killing effect, this could be due to the loss of T helper effect, the specification fails to teach that the CD4+ T cells in the claimed population is cytotoxic. In view of such, the specification fails to support the full scope of the claimed invention.

For reasons of record and set forth foregoing, the specification fails to provide an enabling disclosure commensurate with the scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 36-39, 42, 46-49, 52-55, 84, 89, and 90 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim recitation "a substantially pure population". The amended claims limit the starting cell population to T lymphocytes, however, the term "substantially pure" is not defined by the claim and encompasses considerably wide percentage range for CD4+ and/or CD8+ cells in the total cell population, the specification does not provide a standard for ascertaining the requisite degree of the purity, and one of the skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Upon further consideration, the previous rejections under this provision have been modified, and appear below.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32, 37, 42, 47, 52, 54, 55, 84, 89, 90 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Nair et al* (US 6,306,388 or 6,387,701), as evidenced by *Nair et al* (US 6,670,186).

The details of *Nair et al* '388 and '701 patents have been discussed in the previous Office action, and will not reiterated here. It is noted that the prior art cell population differs from the claimed cell population only by their method of manufacture. However, the method of making the cells as claimed would not distinguish them over the cells taught by the prior art. See *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985), wherein the case law teaches that a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. Accordingly, *Nair et al* anticipate or in the alternative are obvious over the claimed cells.

In 5/14/04 response, Applicants relied on a newly filed Declaration (Kufe Declaration II), and argue the ability of an antigen presenting cell to express MHC class II molecules does not by itself lead necessarily to stimulation of CD4+ cells in the absence of exogenous ligands endocytosed by the APC; but rather the manner in which the antigen is introduced into the APC along with the type of antigen itself determines which of the two possible pathways of antigen processing and presentation are taken by a give antigen.

In response, the scientific fact concerning the antigen processing and presentation for a given antigen is well established in the art. However, Applicants are reminded that the population of immune effector cells disclosed by *Nair et al* is not educated by one given antigen, they were educated by total RNAs or total mRNAs containing coding sequences for many antigens, thus the immune effector cells were educated by multiple antigens in *Nair et al*. Here, all the proper conditions for activating both CD4+ and CD8+ immune effector cells are present, the type of antigen suitable for processing via a MHC class I or II pathway, and APCs capable of processing MHC class I or II antigens (e.g. in the evidence submitted by applicants, *Parkhurst et al* clearly teach, "DENDRITIC CELLS ARE POTENT APCS THAT ARE CAPABLE OF STIMULATING BOTH NAÏVE CD4+ TH CELLS AND CD8+ CTLS" (1st sentence of the cited reference)).

Hence, the subject matter at issue appears to be how dendritic cells process antigens when exposed to total RNAs. To this end, the prior art of record does not appear to have a well-established consent. In the first and second Kufe Declaration, Dr. Kufe asserted that RNA loaded dendritic cells as taught by *Nair et al* would only

activates CD8+ cells via MHC class I antigen processing pathway, because only exogenous antigens that are endocytosed by the antigen presenting cell are presented with class II molecule, citing the chapter authored by Carbone and Beven (§ 7, Kufe Dec. II). The arguments and evidence are not persuasive because there is no evidence of record nor Carbone and Beven conclusively teach how the dendritic cells loaded with total RNA encoding multiple antigens would process the expressed antigens. In fact, in a newly published *Nair* patent '186, they teach, "UPON INTRODUCING RNA INTO AN APC, THE RNA IS TRANSLATED WITHIN THE APC, AND THE RESULTING PROTEIN IS PROCESSED BY THE MHC CLASS I OR CLASS II PROCESSING AND PRESENTATION PATHWAYS" (e.g. column 2, lines 4-10), which would then triggers a chain of events in which the immune system mounts a response to the presented peptides, which would include the activation and expansion of both CD4+ and CD8+ immune effector cells. Accordingly, it appears that the immune effector cells as taught by *Nair et al* would contain both CD4+ and CD8+ cells in the absence of evidence to the contrary.

Applicants are reminded that the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the prior art products do not necessarily or inherently possess characteristics of claimed product, which requires factual evidence demonstrating that actual, unobvious differences exist (or that the claimed products are functionally different than those taught by the prior art) and to

establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPBI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922, 1923 (BPAI 1989).

Moreover, for the sake of argument, assuming the immune effector cell population disclosed by *Nair et al* contains only CD4 or CD8 T cells, it would have been obvious for the ordinary skilled in the art to make a substantially pure population of immune effector cells by combining a CD4+ and a CD8+ T cell population, because it is well known in the art that immune effector cells used for therapy such as cancer immunotherapy often require the presence of both CD4 and CD8 positive cells, and making such cells have become routine in the art as evidenced by *Granucci et al* (6,156,307).

The prior rejection of Claims 32, 37, 42, 47, 52-55, 89, and 90 under 35 U.S.C. 102(e) as being anticipated by *Granucci et al* (6,156,307), is withdrawn, because *Granucci et al* teach stimulating dendritic cells with either class I or class II MHC associated antigens but not both at the same time.

Claims 32, 37-39, 42, 47-49, 52-55, 84, 89, 90 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Inoue et al* (Cancer Res. 1996;56:4702-8).

Inoue et al teach a substantially pure population of educated, tumor antigen specific T lymphocytes obtained from tumor-draining lymph nodes, and isolated by CD3, which containing both CD4+ and CD8+ T cells (e.g. Table 1).

The prior art cell population differs from the claimed cell population only by their method of manufacture. However, the method of making the cells as claimed would not distinguish them over the cells taught by the prior art. See *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985), wherein the case law teaches that a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. Accordingly, *Inoue et al* anticipate or in the alternative are obvious over the claimed cells.

Claims 32, 37-39, 42, 47-49, 52-55, 84, 89, 90 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Schiltz et al* (J Immunother. 1997;20:377-86).

Schiltz et al teach a substantially pure population of educated, tumor antigen specific T lymphocytes obtained from tumor-draining lymph nodes (e.g. pages 378-379), which containing both CD4+ and CD8+ T cells (e.g. Table 4).

The prior art cell population differs from the claimed cell population only by their method of manufacture. However, the method of making the cells as claimed would not distinguish them over the cells taught by the prior art. See *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985), wherein the case law teaches that a product-by-process claim may

be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. Accordingly, *Schiltz et al* anticipate or in the alternative are obvious over the claimed cells.

Claims 32, 37-39, 42, 47-49, 52-55, 84, 89, 90 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Riddell et al* (Review Med Virol 1997;7:181-92).

Riddell et al teach a substantially pure population of educated, viral antigen specific T lymphocytes containing both CD4+ and CD8+ T cells, i.e. T cells used in adoptive transfer to a subject for treating viral infection (paragraph bridging left & right columns, page 184).

The prior art cell population differs from the claimed cell population only by their method of manufacture. However, the method of making the cells as claimed would not distinguish them over the cells taught by the prior art. See *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985), which teaches that a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. Accordingly, *Riddell et al* anticipate or in the alternative are obvious over the claimed cells.

Claim Rejections - 35 USC § 103

Claims 32, 36, 38, 39, 42, 46, 48, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of *Nair et al* (US 6,387,701); or *Schiltz et al* (J Immunother. 1997;20:377-86); or *Inoue et al* (Cancer Res. 1996;56:4702-8), or *Riddell et al* (Review Med Virol 1997;7:181-92), and in view of *Altenschmidt et al* (J Immunol 1997;159:5509-15).

The claims are drawn to genetically modified cytotoxic immune effector cells. The cited references (*Nair et al; Schiltz et al; Inoue et al; or Riddell et al)* teach a substantially pure population of cytotoxic immune effector cells including CD4+ and CD8+ T cells as discussed in detail above, but they do not particularly teach genetically modifying the immune effector cells.

Altenschmidt et al teach genetically modifying immune effector T cells with a chimeric gene encoding zeta-chain of the TCR and a single chain antibody directed against the human ErbB-2 receptor, which provided the T cells with targeted tumor cell-specific recognition (e.g. the abstract)

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the cell populations as taught by *Nair et al; Schiltz et al; Inoue et al; or Riddell et al* by simply modifying the immune effector T cells with a nucleic acid encoding a target cell-specific molecule to enhance the effects of immune effector T cells as taught by *Altenschmidt et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the modification would provide enhanced specificity and thus

increased therapeutic effect. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Applicant's arguments regarding the immune effector cells disclosed in *Nair et al,* and *Granucci et al* have been addressed above, and thus would not be reiterated.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JANICE LI
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Q. Janice Li
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QJL
July 19, 2004